UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/630,383	04/10/96	POULETTY	F A-55320-2/RT

18M1/1127

FLEHR HOHBACH TEST ALBRITTON AND HERBERT
SUITE 3400
FOUR EMBARCADERO CENTER
SAN FRANCISCO CA 94111-4187

EXAMINER	
SCHWADRON, R	
ART UNIT	**PAPER NUMBER**
1816	6

DATE MAILED: 11/27/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire ☒ 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-13 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) any 1-13 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

* U.S. GPO: 1996-410-238/40005

15. Claims 1-12 have been renumbered as claims 1-13 because two claims numbered as claim 6 were present in the instant application.

16. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-3,5-8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending application Serial No. 07/690,530. Although the conflicting claims are not identical, both sets of claims read on the use of the same conjugate and effector system to functionally eliminate a target cell. Claims 1-3,5-7 of the instant application differ in scope from claims 1-5 of copending application Serial No. 07/690,530 in that claims 1-5 read on a method of inactivating a target cell, while claims 1-3,5-8 read on a method of killing a target cell. However, it is obvious that when a cell is killed, said cell is also inactivated. In addition, both sets of claims are drawn to a method for inactivating/killing a target cell in a mammalian host using a conjugate, wherein said conjugate has a moiety that binds a target cell and a moiety that is capable of binding an effector system wherein the effector system is T-cells or endogenous antibody (which acts via an antibody

dependent cytotoxic mechanism). While the scope of claim 1 of Serial No. 07/690,530 differs from claim 1 of the instant application in that it excludes antibodies from the moiety that binds the target cell, it would have been obvious to a routineer that both sets of claims still read on the same nonantibody moieties which can bind target cells (such as ligands for cytokine receptors). With regards to the amount of conjugate used in both sets of claims, because both sets of claims are drawn to methods which have the same ultimate goal (eg. a method for inactivating/killing a target cell), and potentially use identical conjugates (such as the IL-2 containing conjugate which is encompassed by both sets of claims) it would have been obvious to a routineer that similar amounts of conjugate would have been used in both methods. Claim 3 of the instant application simply recites art known superantigens. Therefore, the two sets of claims under consideration in this rejection would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made for the aforementioned reasons.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claim 4 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,4 and 5 of copending application Serial No. 07/690,530 in view of prior art disclosed in the specification (page 9, first paragraph). Paragraph 17 establishes that claim 1 of serial No. 07/690,530 and claim 1 of the instant invention are rejected under the judicially created doctrine of obviousness-type double patenting. Claims 1,4 and 5 of serial No. 07/690,530 do not recite the use of α-gal as the selective moiety in said conjugate. The specification discloses on page 9, first paragraph that Galili et al. teach that antibodies that bind the xenoantigen α-gal were known to occur at high levels in human blood (eg. at levels of 1% of total IgG). Therefore it would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to have used the α-gal in the conjugate of the instant invention, because Galili establishes that endogenous levels of antibody against α-gal are very high, and therefore said endogenous antibodies would have been effective as an endogenous cytotoxic effector system.

This is a *provisional* obviousness-type double patenting rejection.

19. Claim 12 is provisionally rejected under the judicially created doctrine of obviousness-

type double patenting as being unpatentable over claims 6-8 of copending application Serial No 07/690530 in view of Lorberboum-Galski et al.

Although the conflicting claims are not identical, both sets of claims read on the use of the same conjugate and effector system to functionally eliminate a target cell. Claim 12 of the instant application differs in scope from claims 6-8 of copending application Serial No. 07/690,530 in that claims 6-8 read on a method of inactivating a target cell, while claim 12 reads on a method of killing a target cell. However, it is obvious that when a cell is killed, said cell is also inactivated. In addition, both claims are drawn to a method for inactivating/killing a target cell in a mammalian host using a conjugate, wherein said conjugate has a moiety that binds a target cell and a moiety that is capable of binding an effector system wherein the effector system is endogenous antibody. The conjugate used in the method of claim 6 binds to a target cell via the cytokine portion of the conjugate, while the conjugate of claim 12 binds to a target cell via the immunoglobulin fragment portion of the conjugate. Lorberboum-Galski et al. teach that an IL-2 containing toxin conjugate can be used to target lymphocytes expressing the receptor for this cytokine (see Abstract). It would have obvious to a routineer antibody against a T cell surface antigen could have been used instead of IL-2 in the conjugate in the method of claim 6 because both agents function to bind a desired target cell population. Therefore, the two sets of claims under consideration in this rejection would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made for the aforementioned reasons.
This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 9-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,2,4,5 of copending application Serial No. 07/690,530.

Although the conflicting claims are not identical, both sets of claims read on the use of the same conjugate and effector system to functionally eliminate a target cell. Claims 9-11 of the instant application differs in scope from claims 1,2,4,5 of copending application Serial No.

07/690,530 in that claims 1,2,4,5 read on a method of inactivating a target cell, while claims 9-11 read on a method of killing a target cell. However, it is obvious that when a cell is killed, said cell is also inactivated. In addition, both sets of claims are drawn to a method for inactivating a target cell in a mammalian host using a conjugate, wherein said conjugate has a moiety that binds a target cell and a moiety that is capable of binding an effector system wherein the effector system is endogenous antibody. While the scope of claim 1 of Serial No. 07/690,530 differs from claim 9 of the instant application in that it includes target binding moieties and selective moieties other than those recited in claim 9 it would have been obvious to a routineer that both sets of claims still read on the same nonantibody moieties which can bind target cells (such as ligands for cytokine receptors) and the same selective moiety (blood group antigen). While the scope of claim 1 of Serial No. 07/690,530 differs from claim 9 of the instant application in that it includes effector agents other than antibodies, it would have been obvious to a routineer that both sets of claims read on a method where endogenous antibodies can be the effector agent/system. With regards to the amount of conjugate used in both sets of claims, because both sets of claims are drawn to methods which have the same ultimate goal (eg. a method for inactivating a target cell), and potentially use identical conjugates (such as the IL-2 containing conjugate which is encompassed by both sets of claims) it would have been obvious to a routineer that similar amounts of conjugate would have been used in both methods although the particular amount of conjugate is not recited in claim 9. Claim 2 differs from claim 9 in that it reads on a blood group or superantigen as the selective moiety, while claim 9 reads on a blood group or portion of a protein vaccine. However, both claims read on a blood group as the selective moiety. Claims 4 and 10 differ in scope in that interleukins are cytokines, but not all cytokines (eg. CSF) are interleukins. However both claim 4 and 10 read on interleukins. Therefore, the two sets of claims under consideration in this rejection would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made for the aforementioned reasons.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 1-3,5-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9 and 10 of copending application Serial No. 07/690,530.

Although the conflicting claims are not identical, the composition of claims 9 and 10 of

Serial No. 07/690,530 is specifically used or encompassed by compounds that are used in the method of claims 1-3,5-11. The compound used in the methods of the claims of the instant application consists of a moiety (eg. ligand) which binds a membrane receptor, attached to a selective moiety capable of binding an effector system (eg. blood group antigen or superantigen). It would have been prima facie obvious to one of ordinary skill in the art to have used the composition of claims 9 and 10 of Serial No. 07/690,530 in the method of the claims 1-3,5-11 of the instant application because said composition has the same features and properties as the composition used in said method. One of ordinary skill in the art would have prepared the compound used in the method of the instant invention in the form of a composition (eg. including a pharmaceutically acceptable carrier), because said compound needs to be dissolved or incorporated into a vehicle suitable for in vivo administration.
This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claim 12 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9 and 10 of copending application Serial No. 07/690,530.

Although the conflicting claims are not identical, the composition of claim 9 is encompassed by the compound that is used in the method of claim 12. The compound of the method of claim 12 consists of a ligand which binds a membrane receptor (eg. immunoglobulin fragment), attached to a ligand to which antibodies are endogenously present(eg. blood group antigen). With regards to claim 10, while said claim recites that the ligand is IL-2 and not an ATG immunoglobulin fragment, paragraph 19 establishes that claim 12 is obvious over the method which uses the compound of claim 10. It would have been prima facie obvious to one of ordinary skill in the art to have used the composition of claims 9 and 10 in the method of the claim 12 because said composition has the same features and properties as the compound used in said method or is obvious over the compound used in said method. One of ordinary skill in the art would have prepared the compound used in the method of the instant invention in the form of a composition (eg. including a pharmaceutically acceptable carrier), because said compound needs to be dissolved or incorporated into a vehicle suitable for in vivo administration.
This is a *provisional* obviousness-type double patenting rejection because the conflicting claims

have not in fact been patented.

23. Claims 9-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-8 of copending application Serial No. 07/690,530.

Although the conflicting claims are not identical, both sets of claims read on the use of the same conjugate and effector system to functionally eliminate a target cell. Claims 9-11 differ in scope from claims 6-8 in that claims 6-8 read on a method of inactivating a target cell, while claims 9-11 read on a method of killing a target cell. However, it is obvious that when a cell is killed, said cell is also inactivated. Therefore, the two sets of claims under consideration in this rejection would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made for the aforementioned reasons.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 1-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7,11,12 of copending application Serial No. 08/254299. Although the conflicting claims are not identical, both sets of claims read on the use of the same species of conjugate and effector system to functionally eliminate a target cell or reduce the concentration of a soluble target molecule. Therefore, the two sets of claims under consideration in this rejection would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made for the aforementioned reasons.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claims 1-8,12,13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-10 of copending application Serial No. 08/254299. Although the conflicting claims are not identical, both sets of claims read on the use of the same species of conjugate and effector system to functionally eliminate a target cell. Therefore, the two sets of claims under consideration in this rejection would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was

made for the aforementioned reasons.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

27. Claims 9-11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 8-10 of copending Application No. 08/254,299. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. The two groups of claims are identical.

28. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825, however, this application fails to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Applicant is required to fulfill these requirements by defining the SEQ ID NOS in the specification. The following procedure is to be used for cases that contain the same sequence disclosure as the parent. The applicant need not submit a new computer readable form of the Sequence Listing for this CIP application. However, (1) the specification must contain a paper copy of the Sequence Listing, (2) applicant must request in writing that the CRF in the parent case be used to prepare a file for the offspring and (3) applicant must submit a statement that the paper copy of the Sequence Listing in the offspring is identical to the computer readable form submitted

in the parent case.

It is valid to use this approach to bring sequences into rule 60 continuation, divisional or CIPs as long as there are no new sequences (as per this application).

Applicant is required to fulfill these requirements.

Applicant is requested to return a copy of the attached Notice To Comply with the response.

29. The use of the trademarks SEPHADEX, SEPHACRYL, HEVAC, CENTRIPREP, PHARMALINK, PRA, EMAX, SOFTMAX, FICOLL, FACSCAN has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

30. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to use the instant invention for the treatment of disease in vivo in humans. The claims of the instant invention read on a method that the specification discloses can be used for the treatment of human disease in vivo. Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method for human therapy. The state of the art is such that is unpredictable from the in vitro or in vivo mouse data disclosed in the specification as to whether (and how) the instant invention could be used for the treatment of disease in vivo in humans. It is also unpredictable from the in vitro or in vivo mouse data disclosed in the specification as to whether (and how) the instant invention could be used for the treatment of disease in vivo in mammals other than humans. Applicants have provided no working examples with regards to the use of the instant invention for the treatment of disease in vivo in any animal or humans. The in vivo mouse data in the specification relates to the lysis of normal cells and provides no evidence that the instant invention can be used for the treatment of any mouse disease. Applicants have provided no working examples demonstrating that the conjugates used in the method of the instant

invention effect T cell mediated lysis such that a disease is treated in vivo. Applicants have provided no working examples demonstrating that the conjugates used in the method of the instant invention can used to reduce the concentration of a soluble target molecule. With regards to the in vitro data disclosed in the specification, Edgington teaches that in vitro data alone does not establish that a particular agent can be used in vivo in humans for the treatment of disease (see page 386, third column, first and fourth paragraph). With regards to the in vivo mouse data in the specification, Osband et al. teach that the response of animals to immunotherapy is not predictive of the response in humans(see page 193, second column, first paragraph).

With regards to the in vivo use of antibody containing conjugates, Waldmann teaches that the therapeutic use of antibody treatment with any particular antibody/antibody conjugate in humans is unpredictable from in vitro data or in vivo animal data alone. Waldmann states "Despite this wide ranging interest, the "magic bullet" of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved elusive. Only one monoclonal antibody has been licensed for clinical use. "(see page 1657, first column, last paragraph). Waldmann also states that results from clinical studies in humans using antibody based therapeutics for the treatment of cancer did not fulfill the hopes engendered by in vitro studies (see page 1660, second column, last paragraph). Waldmann teaches that the effectiveness of rodent monoclonal antibodies is limited because they "have a short survival time in humans and induce an immune response that neutralizes their therapeutic effect"(page 1658, second column, third paragraph). Waldmann teaches that even human antibodies can be immunogenic by virtue of their idiotypic elements(see page 1659, first column, lines 4 and 5). Harris et al. teach that, "There is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy" and goes on to list problems encountered upon the use of murine antibodies for human therapy (see page 42, second column, first paragraph). Harris et al. also states that, "However, the residual HAMA response to chimaeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective" (see page 42, third column).

With regards to claims that read on a conjugate that contains IL-2 as the ligand for a cytokine receptor on a target cell and a selective moiety that binds a T cell, it is unclear how said conjugate could be used to treat a disease, because T cells capable of mediating killing would also express the IL-2 receptor, and therefore the aforementioned conjugate would bind to a single T cell or bind one normal T cell to other normal T cells and not be available to bind a target cell.

This would also apply to many cytokines, whose receptors are also found on T cells (such as IL-4, IL-6, IL-10, etc.). Furthermore, with regards to the in vivo use of conjugates that contain cytokines, it is unclear as to how the method of the instant invention can inactivate target cells without also inactivating normal cells that express receptors for said cytokine. If the target cell population is present in lesser numbers compared to normal cells which express the relevant cytokine receptor it is also unclear as to whether sufficient quantities of said conjugate would be present to react with a target cell population after interaction with normal cells that possess the pertinent cytokine receptor.

Borrebaeck et al. teach that murine antibodies often contain the α gal antigen (see page 477). Borrebaeck et al. teach that naturally occurring anti- α gal antibodies are found in humans and that said antibodies bind murine monoclonal antibodies when said murine monoclonal antibodies are administered to humans (see page 477, third column first complete paragraph). Borrebaeck et al. teach that , "The presence of anti-Gal antibodies in human serum ensures a quick removal of the xenogeneic mouse mAbs, containing Galα 1-3Gal residues, which results in a lack of antibody mediated effect on neoplastic target cells"(see page 477, third column first complete paragraph). It appears that conjugates containing α gal antigen would also suffer a similar fate and therefore also not be available to mediate lysis of a target cell. Borrebaeck et al. also teaches that the binding of anti-α gal antibodies interferes with the immune function of murine monoclonal antibodies without resulting in any effector function as a consequence of the bound anti-α gal antibodies (see page 477, third column, first complete paragraph, last sentence). The teachings of Borrebaeck et al. seem to indicate that the preformed antibodies (eg. endogenous antibodies) do not act as an immunologic effector system upon binding of said antibodies to an exogenously administered agent , but instead result in the removal of said agent thus preventing the agent from reaching the appropriate target cell.

With regards to claims that read on the use of α gal containing conjugates in mammals, anti-α gal endogenous antibodies are not found in mammals per se, but only in humans and old world monkeys (see Borrebaeck et al., column 1, first indented paragraph). Therefore said conjugates could not be used in mammals per se. In addition, there is no guidance in the specification as to how to determine the dosage of conjugate to use for treatment of a particular disease. There is also no guidance in the specification as to how to determine if an appropriate level of endogenous antibody (eg. endogenous cytotoxic effector) is present so that target cell lysis

could be effected by the administered conjugate.
It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

31. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite in the recitation of "low molecular weight binding protein" because it is unclear what this means or encompasses.

32. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

33. Claims 1,5 and 6 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Segal et al (US Patent 4,676,980) as evidenced by Roitt and Rosen et al.

Segal et al. teach a conjugate that consists of a heteroantibody which possesses a selective moiety which binds a specific receptor on a cytotoxic T cell (an endogenous effector system) and a ligand moiety specific for a surface membrane component which binds said surface membrane component on a target cell (see column 2, last two paragraphs and column 3, third paragraph). Rosen et al. establish that the term "ligand" encompasses an antibody which binds to an antigen (eg. chemical group or molecule bound to another chemical group or molecule). A surface membrane receptor is a surface membrane component on a target cell. Segal et al. teach that the selective moiety which binds a specific receptor on a cytotoxic T cell should bind the receptor on the cytotoxic cell which is responsible for triggering lysis (see column 3, lines 5-7). Roitt establishes that the art recognized that this refers to the antigen recognition moiety of the T cell, which is the T cell receptor (see page 48). In addition, Segal teaches that the antibodies can be

directed against the receptor or the receptor complex on the cytotoxic which is responsible for triggering lysis (see column 3, lines 5-7) and that a heteroantibody against T3 can be used in the conjugate (see last paragraph, column 6). Roitt (page 48) establishes that the art recognized that T cell receptor complex also includes T3, indicating that the receptor on the T cell referred to by Segal et al. is the T cell receptor. Segal et al. teach that when the conjugate is bound to the T cell and the target cell, that said target cell is lysed (see column 3, third paragraph). Segal et al. teach that the conjugate can be used to direct the "normal immune system to attack specific targets in vivo"(column 1, fourth paragraph from the bottom) and that these conjugates can cause normal cytotoxic cells to "inactivate a specific cell type" (column 1, third paragraph from the bottom). Segal teaches that this method can be used in a mammalian host (column 13, last paragraph). Segal et al. teaches the amount of conjugate to be used to substantially inactivate a target cell population (see column 14, first paragraph).

34. Claims 1-6,12 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Pouletty (EP 0510949).

The xenoantigen of claim 2 is not disclosed in parent application 07/690530, therefore with regards to prior art for this claim the priority date is taken as the filing date of application 08/254,299. The low molecular weight binding molecule of claim 6 is not disclosed in parent application 07/690530 or 08/254,299, therefore with regards to prior art for this claim the priority date is taken as the filing date of the instant application. The SEB or MLs of claim 3 are not disclosed in parent application 07/690530, therefore with regards to prior art for this claim the priority date is taken as the filing date of the application 08/254,299. The method of claim 1 reciting proviso (b) is not disclosed in parent cases 07/690530 or 08/254,299, therefore with regards to prior art for this claim the priority date is taken as the filing date of the instant application. The method of claim 12 using antibody against any T cell molecule is not disclosed in parent cases 07/690530 or 08/254,299, therefore with regards to prior art for this claim the priority date is taken as the filing date of the instant application. Pouletty teaches the method of the instant invention wherein the selective moiety is a blood group antigen (see column 2, paragraphs one through four). Pouletty teaches the method of the instant invention wherein the selective moiety is the superantigen SEA (see column 4, first incomplete paragraph). Pouletty teaches the method of the instant invention wherein a ligand is used as the moiety specific for a

cell surface receptor (see Abstract).

35. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35. Claims 1 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ochi et al., 1987 as evidenced by Roitt.

The claims are drawn to the method of claim 1 and 6. Ochi et al. teach a conjugate that consists of KLH covalently linked to an anti-id monoclonal antibody (anti-id-KLH complex)(see page 1645, second column, section 2.2, continued on page 1646). The anti-id monoclonal antibody part of the conjugate is a moiety specific for a surface membrane receptor on a target cell in that it binds a specific B cell lymphoma (the target cell) that expresses the appropriate surface immunoglobulin (a receptor) (see Abstract, page 1645). The KLH part of the conjugate is a selective moiety which binds a specific receptor on a T cell in that KLH is the antigen that the aforementioned T cell specifically recognizes (see Abstract). Roitt establishes that the art recognized that specific recognition of antigen by T cells is accomplished by the T cell receptor (see page 48). Therefore the T cell receptor is binding the KLH portion of the conjugate. Ochi et al. teach that when the conjugate is bound to the target cell and the T cell, that the target cell is killed (see page 1645, column one). Ochi et al. teach that said conjugate can be used to kill target cells in vitro (Figure 1, page 1646). Ochi et al. teach that said conjugate an be used to kill target cells in vivo (the reference to clearance of lung metastatic tumors in this sentence from Ochi et al. means that the tumor cells were killed) (page 1647, second column, next to last sentence). It would have been obvious to a routineer that when tumor cells are killed, these tumor cells are

inactivated. Ochi et al. teaches that the method using said conjugate to kill target cells was performed in vivo (page 1647, second column, next to last sentence). The KLH specific T cells which kill the A20HL tumor cells in vivo are an endogenous cytotoxic effector system. While Ochi et al. do not specifically teach that the in vivo experiments were performed in a mammalian host, it would have been obvious to a routineer that since the in vitro experiments taught by Ochi et al. were performed in mice using mice cells, that the in vivo experiments were also performed in mice (a mammalian host). Therefore the method of the instant invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

36. Claims 2 and 3 are rejected under 35 U.S.C. § 103 as being unpatentable over Ochi et al., 1987 as evidenced by Roitt as applied to claim 1 above, and further in view of Dohlsten, 1990 and Pullen.

The claims are drawn to the method of claim 1 wherein the selective moiety is a superantigen and the superantigen is one of the superantigens recited in claim 3. Ochi et al. makes obvious the method of the instant invention, but not the use of a superantigen as the selective moiety (see paragraph 35 of this Office Action). Dohlsten et al. teach that staphylococcal enterotoxins (SE) can be used to direct T cells to mediate cytotoxicity against target cells that a particular T cell with a particular specificity would not ordinarily bind (see Summary, page 96, and page 97, *Results* section). Dohlsten teaches that SE also binds MHC class II on target cells and that this binding is involved in the mechanism wherein SE bound T cells are directed to a particular target(see page 99, first column). Pullen teaches that staphylococcal enterotoxins were known in the art as superantigens (see page 1365, first column, first paragraph). Dohlsten teaches that SEA, SEB or SEC1 could mediate T cell killing of target cells (see page 98, second column). Dohlsten teaches that different SEs (such as SEA, SEB or SEC1) activate different T cells (see Figure 3), so that a routineer would have used a particular SE or combination of SEs depending on the particular T cell population that was to be used in the method. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the method of the instant invention by using the SE taught by Dohlsten et al. as the selective moiety in the method taught by Ochi et al. because the method of Ochi et al. depends on the use of a particular T cell which recognizes a particular antigen (eg. KLH), while SE will bind a variety of different T cells regardless of the antigen specificity, thus

removing the need for the specific T cell which recognizes a specific antigen as per the method taught by Ochi et al. In addition, Dohlsten et al. teach that SE can be used to kill MHC II target cells (page 100, first column, last sentence). Therefore, by attaching the SE to the conjugate taught by Ochi et al., the SE conjugate can also be used to direct T cells to kill target cells that express antigens other than class II (eg. any antigen that was bound by the antibody portion of the conjugate taught by Ochi et al.). One of ordinary skill in the art would have a reasonable expectation of success for the aforementioned reasons.

37. Claim 4 is rejected under 35 U.S.C. § 103 as being unpatentable over Pouletty (EP 0510949) in view of prior art disclosed in the specification (page 9, first complete paragraph).

The α-gal xenoantigen of claim 4 is not disclosed in parent application 07/690530, therefore with regards to prior art for this claim the priority date is taken as the filing date of the application 08/254,299. The claim is drawn to the method of claim 1 wherein the selective moiety is α-gal. Pouletty teaches the method of the instant invention (see column 2, paragraphs one through four) except for the use of α-gal as the selective moiety. Pouletty teaches that the selective moiety of the conjugate can be a moiety that binds an antibody and that said moiety can include antigens to which naturally occurring antibodies are present in the host (see column 3, last paragraph). The specification discloses that antibodies that bind the xenoantigen α-gal were known in the art to occur at high levels in human blood (eg. at levels of 1% of total IgG)(page 9, first complete paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the α-gal xenoantigen in the method taught by Pouletty because antibodies against α-gal xenoantigen were known to occur in large quantities in human blood, and therefore conjugates containing α-gal xenoantigen would have been strong mediators of antibody mediated lysis of target cells because large amounts of antibodies against α-gal were present in the circulation. One of ordinary skill in the art would have a reasonable expectation of success for the aforementioned reasons.

38. No claim is allowed.

39. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-7939.

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00.
The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1816
November 22, 1996

Application No. 08/630383

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.82 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitte However, the content of the computer readable form does not comply with the requirement of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has bee found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☒ 7. Other: See enclosed office Action (paragraph 28)

Applicant must provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the s and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please conta

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.